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Case Report Open Access

Leucopenia in Acute Myeloid Leukemia Presenting as Myocardial Infarction: A Case Report

Harold K Elias[1], Nawaz Mohammed[1], Vanamala AA[2], Karuna R Kumar[2] and Arun S Shet[1,3]*

[1]*Department of Medical Oncology, St. Johns National Academy of Health Sciences, Bangalore 560034, India*
[2]*Department of Clinical Pathology, St. Johns National Academy of Health Sciences, Bangalore 560034, India*
[3]*Hematology Research Unit, St. Johns National Academy of Health Sciences, Bangalore 560034, India*

Abstract

Thrombotic complications are known as accepted feature of acute myeloid leukemia and tend to occur in patients with hyperleucocytosis. Acute myocardial infarction, though reported is a rare clinical presentation in patients with this subtype of leukemia. We describe an unusual case of acute myeloid leukemia in a patient with leucopenia presenting with an acute myocardial infarction. The possible mechanisms underlying the pathogenesis of myocardial infarction in a patient without atherosclerotic coronary artery disease are reviewed.

Keywords: Leucopenia; Myocardial infarction; Leukemia; Leucostasis

Introduction

Hyperleucocytosis defined as total leukemia blood cell count greater than 50-100×10^9/L results in thrombotic complications such as stroke, acute myocardial infarction (AMI) and thromboembolism. Hyperleucocytosis occurs in 8.5% of leukemia cases, and is most commonly observed in childhood T cell-acute lymphoblastic (T-ALL) [1], acute myeloid leukemia (AML) especially monoblastic (FAB-M5), myelomonocytic (FAB-M4) or the microgranular variant of acute promyelocytic leukemia (FAB-M3) [2], chronic lymphoid leukemia and blast crisis of chronic myeloid leukemia (CML). However, rarely patients do present with thrombotic complications in the absence of hyperleucocytosis or even elevated leukocyte counts. Here we report the case of a 32 year old male who presented with an AMI associated with leucopenia and was subsequently diagnosed to have AML not otherwise categorized. The clinical and pathological findings of this case and the possible mechanisms of AMI in the absence of occlusive coronary artery disease are discussed.

Case Report

A 32 year old gentleman with no antecedent hematological disorder was admitted to the state cardiac center with acute onset severe chest pain lasting greater than 12 hours. The admission EKG showed normal sinus rhythm with ST segment elevations in the anterior chest leads and along with his raised cardiac enzymes (creatine phosphokinase-MB and cardiac troponin-I) confirmed an acute myocardial infarction. Bedside echocardiography revealed an akinetic apico anterior segment, reduced left ventricular function (EF=36%) and a left ventricular apical clot. The patient underwent an emergent coronary angiogram which showed a subtotal thrombotic occlusion of the proximal segment of his left anterior descending artery but no obvious atherosclerotic lesions in his coronary vessels. Since the patient had presented beyond the window period for thrombolysis, he was managed with antiplatelet agents, ACE inhibitors and low molecular weight heparin. Hemoglobin and platelet counts at admission were normal but unexpectedly revealed leucopenia with absolute neutropenia 2.3×10^9/L (differential counts were: neutrophils 20%, lymphocytes 51%, monocytes 28%, and eosinophils 2%]. As his remaining hematological, biochemical and coagulation parameters were normal, this incidental finding was attributed to a recent viral infection he had been convalescing from and was hence subsequently discharged.

Over the next few weeks, he presented with two episodes of fever with lower respiratory tract infection and his neutropenia which did not undergo bone marrow evaluation at the time of his previous admission, persisted. The patient was hence referred for hematological evaluation at our center where a bone marrow examination revealed a hypocellular marrow with 65% blasts that stained positively for myeloperoxidase with no evidence of dysplasia. Based on morphological and flow cytometric findings, the patient was diagnosed with acute myeloid leukemia (AML) otherwise not categorized, Acute myeloid leukemia with maturation (WHO classification). There was no evidence of numeric or structural chromosomal abnormality based on traditional karyotyping studies. Chest radiography and ultrasound of the abdomen were normal at admission. The patient was counseled and initiated on standard induction chemotherapy with Daunorubicin (45 mg/m^2) and Ara-C (200 mg/m^2) for 3 days and 7 days respectively. Post induction on day 10, he developed febrile neutropenia and a CT scan chest showed minimal pleural effusion with nodular pulmonary opacities. He was initiated on broad spectrum antibiotics and therapeutic doses of amphotericin B for presumed fungal pneumonia. A thoracocentesis with pig tail insertion was performed on Day 14; however, the pleural fluid did not yield any growth on culture. A subsequent CT scan guided aspiration of the most peripherally accessible pulmonary nodule yielded 10 ml of hemorrhagic fluid that did not grow bacteria or fungi on culture. However, the patient appeared to respond to antibacterial and antifungal therapy with improvement in clinical and radiological parameters. On day 27, a post induction marrow aspirate and biopsy performed following adequate hematological recovery (ANC >1.0×10^9/L and a platelet count >100×10^9/L) showed a hypo cellular marrow with <1% blasts suggestive of complete remission. The patient was discharged on oral voriconazole as empiric therapy for

***Corresponding author:** Arun Shet, Professor of Medicine, Hematology and Oncology Head, Department of Medical Oncology, St Johns Medical College and Hospital, Sarjapur Road, Bangalore 560034, India, Tel: +91 80 2206 5744; Fax: +91 80 2206 5744; E-mail: arunshet@sjri.res.in, arunshet1@gmail.com

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aspergillus during which his pulmonary lesions improved. Within 10 days of discharge, he was readmitted for consolidation chemotherapy with high dose cytarabine. However, during this therapy the patient developed neutropenic sepsis and expired.

Discussion

Several pathological mechanisms for acute MI without underlying coronary atherosclerosis have been described in patients with leukemia [3]. These typically follow one or more of the following: 1. Leukemic infiltration into the myocardium or pericardium [4-7]. 2. Antileukemic therapy with chemo or radiotherapy resulting in leukostasis due to increased adhesivity or decreased deformability of the leukemic blasts. 3. Disorders of blood coagulation [6,7]. 4. Leukemic plugging by clumps of blasts causing occlusion of a major coronary vessel [6,7].

Our patient presented with acute anterior wall MI and was found to have a thrombotic occlusion of the left anterior descending artery on coronary angiography. Although leukemic thrombi are a well-known complication of acute or chronic myeloid leukemia, they tend to occur most commonly in the setting of hyperleucocytosis when the leukemic cell burden is very high i.e. (>100,000/µl or higher) [8-10]. Interestingly, Cadelpergher et al. [6], Jachmann-Jahn et al. [11] have reported AMI in the setting of AML with normal leucocyte counts suggesting that a high number of circulating blasts is not an absolute requirement for thrombotic coronary occlusion. Seminal works by Lichtman and Rowe [12], demonstrated an in-vitro model of leukostasis by showing an increased viscosity (leukocrit) in leukocyte suspensions (12-15 mL/dL), which he suggested may alter the blood rheological properties thereby compromising tissue perfusion. However, elevated leukocyte counts necessary to explain such raised leukocrit values are seldom observed clinically. He subsequently provided additional experimental evidence to confirm that leukostasis is perhaps, initiated in the microcirculation. Over time, the increased ischemic stress may manifest either due to enhanced production of inflammatory cytokines and up regulation of cell adhesion molecules (ICAM, VCAM, E, P & L-selectins) in the malignant blasts, or modulation in adhesivity between leukemic blasts and the vascular endothelium.

Leukemic blasts are relatively less deformable in comparison to their mature myeloid counterparts and become even less so after chemotherapy induced changes in the actin cytoskeleton [13], which may reduce deformability and promote circulatory stasis and obstruction [11]. The resulting rheological effects of circulating blasts and local hypoxemia play a major influence in promoting enhanced endothelial cell-interactions, by the concomitant upregulation of several adhesion molecules (CD54, CD62E, CD106, CD62P) on endothelial cells and its interactions with chemokines such as interleukin-8 [14,15]. In addition, increased levels of cytokines IL1β, IL6, and TNF-α in leukemic blasts have a proinflammatory effect, resulting in further endothelial damage with an increased expression of adhesion markers on the endothelium [16]. Such a paracrine feedback loop has been shown to up regulate endothelial surface expressing selectins (E and L selectins) [17] and integrins (ICAM-1, V-CAM1) [1,16,17] and even tissue factor (the trigger of coagulation *in vivo*) [18,19]. Increased expression of cellular adhesion molecules could then result in ligand binding with subsequent adhesion [18,19].

Coagulation dysfunction often results in thrombosis and possibly disseminated intravascular coagulation but is more well accepted in patients with acute promyelocytic leukemia which this patient did not have (absent 15-17 translocation) [20-23]. Typically, in this setting coagulation occurs due to release of tissue factor from malignant promyelocytic and results in disseminated intravascular coagulation. In patients with atherosclerotic coronary artery disease, rupture or fissuring of an atherosclerotic plaque results in exposure of procoagulant tissue factor like material which immediately triggers the coagulation system and results in thrombotic occlusion of a major coronary vessel. A more localized form of coagulation dysfunction due to abnormal endothelial tissue factor expression in the coronary bed (either resulting from endothelial injury or the effect of proinflammatory cytokines) is a possibility in our patient [23-26]. Finally, leukemic infiltration of the endocardium and myocardium with subsequent thrombosis is a possibility, however we were unable to test this hypothesis as a cardiac biopsy was not performed. Thus, one may speculate that with leucopenia, these abnormally altered adhesive leukemic blasts disrupt the oxygen tension in the microcirculation. Eventually, this switches on a cascade of inflammatory signals, causing endothelial injury, tissue factor expression, which in effect culminates into a thrombotic vascular occlusion in a major coronary vessel in the absence of underlying atherosclerosis [13,23,24].

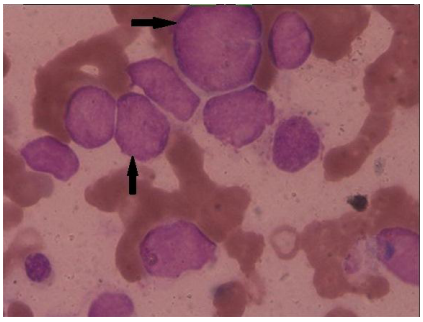

Figure 1: Bone Marrow smear showing mature myeloblasts with scanty coalescent granules and basophilic cytoplasm (depicted by black solid arrows).

Although rare, the published literature suggests that AML presenting with AMI is associated with normal or elevated leukocyte counts [7,8,10,12,26] which apparently causes leucostasis and subsequent thrombotic vessel occlusion. This case, to the best of our knowledge represents the first AMI in the setting of AML associated with leucopenia. The finding that thrombotic arterial occlusion is possible even in leucopenic AML patients suggests that factors apart from elevated counts such as, an inherent adhesivity of abnormal blasts due to abnormally overexpressed cellular adhesion molecules or abnormal tissue factor expression is contributory to the underlying mechanism of thrombotic vascular occlusion in AML.

Conclusion

Even in the absence of high leucocyte counts, AML can cause thrombotic vascular occlusion. The underlying mechanisms for this manifestation include morphological alterations, increased adhesiveness of leukemic blasts, altered macro and micro circulatory rheology and abnormal expression of endothelial adhesion or coagulation molecules possibly due to the effects of proinflammatory cytokines. These mechanisms either singly or in concert could promote cellular cross talk between the leukocyte and endothelium that triggers thrombosis *in vivo* resulting in vascular occlusion (Figure 1).

Contributions

HKE: drafting of the manuscript and patient care. MN: data gathering and patient care. VAA & KRK: pathological analysis of patient samples. ASS: patient care, drafting and final approval of the manuscript.

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